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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/776,044	02/26/97	BYWATER M	1614-178P

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BIRCH STEWART KOLASCH AND BIRCH
PO BOX 747
FALLS CHURCH VA 22042-0747

EXAMINER	
EYLER, Y	
ART UNIT	**PAPER NUMBER**
1642	11

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/776,044	Applicant(s) Bywater et al.
	Examiner Yvonne Eyler	Group Art Unit 1642

☒ Responsive to communication(s) filed on *Nov 10, 1998* .

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-11 and 13* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-11 and 13* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

Response to Amendment

Claims 1-11 and 13 are pending and under consideration in the application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Objections

1. The objection to Claim 10 is withdrawn.

Claim Rejections Withdrawn:

2. All rejections of Claim 12 are withdrawn in light of the cancellation of the claim.

3. The rejection of Claims 1 and 5-9 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in light of the amendments to the claims.

Claim Rejections Maintained:

4. The rejection of Claims 2-4, 10, and 11 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is maintained.

Claim 2, as now written, includes an improper Markush Group which makes it unclear. This may be overcome by indicating that the mutation is selected from the group consisting of...

Claim 4, as now written recites "a part or parts or the ...."

Claim 10 now reads "The method claim 1" rather than -the method of claim 1- Claim 10 is also vague and indefinite in the recitations of "preparing" DNA, amplifying "at least part", and "processing the gene with sequencing reactions" because the metes and bounds of the activities encompassed cannot be determined. It is not clear what activities are performed in order to "prepare" DNA. The metes and bounds of DNA amplification are clear, however, it is not clear how much DNA a part is. Finally, it is not clear what activities are performed in order to process the DNA. One suggestion of clear claim language would be:

The method of claim 1, comprising one or more of the following steps:

a) obtaining a genomic DNA or cDNA sample

b) amplifying the sequences corresponding to the cancer-related p53 gene

c) sequencing the sequences obtained in step b.

d).....

This is also true of claim 11, in that the metes and bounds of "preparing" DNA, amplifying "at least a part" of DNA, and "processing" the DNA cannot be determined.

5. New Claim 13 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention as detailed above for claims 2-4, 10, and 11 because new claim 13 does not clarify the issues detailed above.

6. Claim 2 and dependent claim 3 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 2 now recites limitations which were not clearly disclosed in the specification, as filed, and now change the scope of the disclosure. Such limitations recited in the present claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112. Applicant points to pages 3 and 5, however, page 5 discloses that the p53 gene is analyzed for point mutations, deletions, or insertions but does not include missense or nonsense mutations. Page 3 discloses that missense mutations are common in p53 and thus the detection of these is reasonably supported by the disclosure. However, there is no support found at either page 3 or 5 for detection of nonsense mutations which are taught at page 3 to apply to Retinoblastoma, not p53.

7. The rejection of Claims 1-11 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is maintained.

Applicant argues that the specification is enabling for prognostication of neoplastic development and determination of guidance for treatment by determining the combination of the presence of p53 mutations and node status. Applicant lists each of the 4 subgroups of

p53mutations/node status and the prognosis and treatment indicated by each. Applicant then argues that each of the 4 subgroups is prognostic and provides guidance.

This argument has been considered but is not found to be commensurate in scope with the claimed invention. Applicant appears to have mischaracterized the basis of the rejection. Applicant has argued with regard to the scope that was stated to be enabled. The specification enables prognostication and provides guidance for treatment when each of the 4 subgroups are considered. This is not what is claimed, however. The claims are not limited to determination of p53 mutation/node status combination. The claims encompass determination of any mutation in p53, at any location, plus determination of node status, but the correlation step of the claimed invention does not put the combination together as applicant argues. Rather the correlation step simply uses any determined information to prognose and guide. There is insufficient objective evidence and guidance regarding prognostication and treatment determination encompassing the scope of using any information gleaned for steps a-c.

8. New Claim 13 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the reasons detailed above and in the office action of 6/10/98 with regard to claims 1-11.

Claim 13 depends from claim 11 but does not overcome the issues detailed above and in the Office Action of 6/10/98.

9. The rejection of Claims 1-8 under 35 U.S.C. 103(a) as being unpatentable over Elledge et al. (Breast Cancer Res. Treat. 27:95-102, 1993) in view of Callahan (J. Natl.Cancer Institute. 84:826-827, 1992) and as evidenced by Hartmann et al. (TIG 13:28, 1997) is maintained.

Applicant argues that Elledge et al. teach determination of p53 mutations by SSCP and do not teach the sequencing of all samples. Applicant further argues that SSCP is not as accurate as sequencing and thus the instant invention is an unobvious improvement over that of Elledge et al. Secondly, applicant argues that the final statement of Elledge et al. teaches away from the combination of p53 mutation and node status, indicating that it is not a reliable indicator. Finally, applicant argues that Callahan is merely an editorial and inaccurately speculates regarding the value of prognosis and treatment guidance using the combination of p53 mutations and node status.

These arguments have been considered but are not found to be persuasive. Claim 1 and dependent claims thereof, indicate that the DNA sequence is analyzed to determine mutations. Elledge et al. does this. There is no limitation that sequencing per se be performed. However, Elledge et al. does sequence samples to determine p53 mutation, indicating that sequencing of p53 DNA in cancer samples to determine prognosis and treatment was known in the art at the time the invention was filed. Applicant further argues sequencing DNA samples rather than performing SSCP analysis provides a superior method due to the inefficiency of SSCP analysis. There is,

however, no objective evidence provided to support this conclusion, which cannot therefore, be evaluated. Further, an unexpected advantage or superior performance must be disclosed at the time of filing. The instant specification discloses that the determination of p53 mutation at the DNA level is superior to histochemical determination and that the combination of p53 mutation and node status is superior to either alone. There is no disclosure in the specification regarding superiority of sequencing, however. Neither is there any indication that, based on the teachings of Elledge et al. that both SSCP and sequencing result in determination of p53 mutation, that it would not have been an obvious choice by one of ordinary skill in the art to utilize either one in the determination of p53 mutation.

Applicant has further argued that Elledge et al. teach away from the combination of node status and p53 mutation in provide prognostic information and guidance based on the final sentence of the reference. Elledge et al., however, teach that the goal of their research was to determine if the combination of p53 mutation and node negative status was indicative of a good prognosis and as an indicator of development of micrometastasis. Elledge et al. found that the combination of p53 mutation and node negative status was a poor prognostic indicator, with a higher risk of relapse (see page 98, column 1, lines 5-10). Thus, Elledge et al. conclude that node negative/p53 mutant groups do not define a group in which not giving (i.e. withholding) adjuvant therapy is advised. Elledge et al. teach that p53 mutation combined with node negative status indicate a prognosis of relapse and provide guidance that adjuvant therapy is required.

Callahan was cited for the suggestion of combining node status and p53 mutation as prognostic of breast cancer. This would include determining p53 mutation and determining node status together, not just determining p53 mutation in node negative patients only as taught by Elledge et al. Applicant argues that Elledge et al. teaches away from the prognostic method taught by Callahan, however, this is not found to be persuasive as discussed supra. In the absence of objective evidence to the contrary, Callahan's teachings are maintained to be an accurate reflection of the state of the prior art and it is maintained that it would have been *prima facie* obvious to one of ordinary skill in the art to combine, with a reasonable expectation of success, the sequence-based p53 analysis of Elledge et al., including analysis of functional domains, including a DNA binding domain, with art standard nodal status assays, as taught by Callahan to prognostically classify neoplasia and one would have been motivated to do so in order to facilitate identification of patients in need of more aggressive postsurgical therapy as taught by Callahan.

10. The rejection of Claim 9 under 35 U.S.C. 103(a) as being unpatentable over Elledge et al. (Breast Cancer Res. Treat. 27:95-102, 1993) in view of Callahan (J. Natl.Cancer Institute. 84:826-827, 1992) and as evidenced by Hartmann et al. (TIG 13:28, 1997) as applied above to claims 1-8 and further in view of Mitsudomi et al. (J. Nat. Cancer Inst. 85:2018-2023, 1993) is maintained.

11. The rejection of Claims 10-11 under 35 U.S.C. 103(a) as being unpatentable over Elledge et al. (Breast Cancer Res. Treat. 27:95-102, 1993) in view of Callahan (J. Natl.Cancer Institute. 84:826-827, 1992) and as evidenced by Hartmann et al. (TIG 13:28, 1997) as applied to

claims 1-8 above and further in view of Hedrum et al. (BioTechniques, 17:118-129, 1993-IDS) is maintained.

Applicant chooses to argue the rejection of claims 9, 10, and 11 together, and thus these rejections will be addressed together.

Applicant reiterate that argument addressed above, that Elledge et al. does not teach the advantage of sequencing over SSCP analysis of p53 mutation and thus there is no suggestion to combine the teachings of the art. This is not found to persuasive, as discussed supra and further, Hedrum et al. support that sequencing of p53 as a means of determining mutation was known in the art at the time the invention was made.

12. New Claim 13 is rejected under 35 U.S.C. 103(a) as being unpatentable over Elledge et al. (Breast Cancer Res. Treat. 27:95-102, 1993) in view of Callahan (J. Natl.Cancer Institute. 84:826-827, 1992) and as evidenced by Hartmann et al. (TIG 13:28, 1997) as applied to claims 1-8 above and further in view of Hedrum et al. (BioTechniques, 17:118-129, 1993-IDS) for the reasons detailed above with regard to claims 10 and 11 and in the Office Action of 6/10/98.

Claim 13 specifies only that the automated sequencing be solid-phase based, which taught by Hedrum et al. To reiterate: Elledge et al. and Callahan teach as set forth above but do not teach the use of automated, computer-aided or solid phase sequencing techniques.

Hedrum et al. teach the use of automated, robotic workstations in amplification and solid phase sequencing of p53 DNA to detect mutations for prognostic information. See the abstract; and page 118, column 3.

Therefore, it would have been *prima facie* obvious to and one of ordinary skill in the art would have been motivated to automate the assay of Elledge et al. as modified by Callahan., with a reasonable expectation of success as taught by Lindstrom and Hedrum et al. in order to streamline and analyze multiple samples for prognostic information.

NO CLAIM IS ALLOWED.

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yvonne Eyler, Ph.D. whose telephone number is (703) 308-6564. The examiner can normally be reached on Monday through Friday from 830am to 630pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paula Hutzell, can be reached on (703) 308-2731. The fax phone number for this Group is (703) 305-3014 or (703) 308-4242.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [**paula.hutzell@uspto.gov**].

All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Yvonne Eyler, Ph.D.
Patent Examiner
January 26, 1999

Sheela J. Huff

SHEELA HUFF
PRIMARY EXAMINER